January 30, 1961

Dr. A. Lima-de-Faria
Institute of Genetics
University of Lund
Lund, Sweden

Dear Doctor Lima-de-Faria:

This is in reply to your letter of January 12 and the accompanying manuscript "Selection at the molecular level." I am flattered that you should refer your paper to me prior to submitting it to Science. However, I am forwarding it to the editor, Dr. Graham DuShane, in the regular procedure - it will doubtless be reviewed by an anonymous referee to determine its suitability for publication.

For my own part, I have found this an interesting discussion. The only remark that I would quarrel with is the one on your page 12, that "organism selection . . . is only of secondary importance." Of course it is secondary in the sense that it can only apply to those mutations that have survived long enough to be represented in the genotype of a new organism but I wonder if you also mean to imply that it is of subsidiary importance in determining the existing character of evolved life. With regard to the following paragraph, I would look on the same problem from a slightly different standpoint, that the chromosome itself is an organ for the functioning of which some of the genes it contains are of immediate relevance. For example, a mutation that impaired the synthesis of the enzyme DNA synthetase would be lethal to the nucleus in which it first became manifest long before any complete 'organism' could develop with a corresponding phenotype. I would also accept, as you suggest, that there are many other determinants of chromosomal function per se, whose integrity and coordination are essential for the survival of the cell. On the other hand, I believe that it may be an overstatement to suggest that every nucleotide substitution is subject to the same kind of selection. I would assume that from the standpoint of the immediate mechanism of replication that "the molecular array of a chromosome is indeed a meaningless assortment of letters," and that the message only has significance when it can be translated via the imprint on RNA and the synthesis of protein. However, this is a question that may soon be susceptible to experimental test, for example, the determination of the fraction of nucleotide alterations in chemically treated DNA that impair the capacity of that DNA molecule to replicate either in an in vitro enzymatic system or in some system of infection by phage or transfer DNA as bacterial transformation.

I am trying to think of some other particular cases where chromosome selection has been evident. The recent examples of meiotic drive that Sandler and Crow have discussed may be relevant; I also recall an example that Auerbach published on a defective centromere in Drosophila. In one of my own first works with F. J. Ryan, we considered the possibility of nuclear

competition within a heterocaryotic hypha of Neurospora. But it is still an open question whether this is the correct explanation or whether the selection occurs at the level of homocaryotic branches arising by random assortment of nuclei. Frankly, I would believe that explicit examples suggesting the operation of chromosome selection are more pertinent than the evidence of local individuality that you have cited in the paper and which is doubtless useful in framing the problem. On the whole, the main argument may be one of emphasis, whether the word chiefly, which appears at the close of your quotation on page 6 would be better justified than "partly." My own immediate reaction would be to give greater emphasis to this process for structural changes than has been customary in the past but to consider it less important for the fate of single nucleotide substitutions. On the second point, as I have indicated, the experiments should soon be decisive.

May I thank you for having continued to send me your publications and for your courtesy in letting me see this one.

Yours sincerely,

Joshua Lederberg
Professor of Genetics

Cf: Ryan, F. J. and J. Lederberg, 1946. Reverse-mutation and adaptation in leucineless Neurspora. Proc. National Acad. Sci 32: 163-173.

Pittenger, Thad H. and K. C. Atwood, 1956. Stability of nuclear proportions during growth of neurospora heterokaryons. Genetics 41: 227-241.

Auerbach, C., 1947. Abnormal segregation after chemical treatment of Drosophila. Genetics 32: 3.

Sandler, L., Yuichiro Hiraizumi and Iris Sandler, 1959. Meiotic drive in natural populations of Drosophila melanogaster. I. The cytogenetic basis of segregation-distortion. Genetics 44: 233-250.